REVIEW ARTICLE

Pharmaceutical Activities and Effects of Various Abiotic Stresses/Elicitors on Bioactive Constituents of *Psoralea corylifolia* L. (Bakuchi)

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Abstract

Psoralea corylifolia is an endangered and traditionally important medicinal plant of the family Fabaceae. It is used worldwide for the treatment of several ailments due to presence of various bioactive constituents that are mainly concentrated in seeds and fruits of plant. This review is an attempt to summarize the various pharmaceutical activities possessed by *P. corylifolia* and the effect of several abiotic stresses or elicitors on the bioactive constituents of the plant.

Keywords: *Psoralea corylifolia*, Pharmaceutical activities, Abiotic elicitors, Psoralen, Bakuchiol

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Introduction

According to World Health Organization (WHO) approximately 80 percent of world's population depends on plant-based products for their primary health care (Uikey *et al*., 2010). The use of medicinal plants have increased day by day throughout the world with the pressing demand for herbal drugs, natural health products and secondary metabolites of medicinal plants (Cole *et al*., 2007). *Psoralea corylifolia* is an endangered medicinally important plant of the family Fabaceae. It is commonly called as bakuchi, babchi, bavachi, Bu Ku Zhi, Ku Tzu, buguzhi (Khusboo *et al*., 2010). The name *Psoralea* is taken from the Greek term *psoraleos*, that means "affected with the itch or with leprosy" (Zhang *et al*., 2016). It is widely distributed in the tropical and subtropical region of the world. It is distributed throughout India in Himalayan region, Dehra Dun, Bundelkhand, Bengal, Bombay, Karnataka, semi-arid region of Rajasthan, Punjab, Uttar Pradesh and Madhya Pradesh (Sharma *et al*., 2001; Sah *et al*., 2006). It is an erect annual herb, grows up to the height of 30-180 cm and found as a common weed. The leaves are petiolate, stipulate, simple, broadly elliptic to rounded, serrate, mucronate at the apex, gland dotted covered with several small white hairs at both the surfaces, and five main nerves arise from the base of leaves (Khusboo *et al*., 2010). Stem are grooved and covered with small white hairs. Inflorescence is an axillary racemose, raceme having 30-40 small, purple white and papilionaceous flowers. Flowering generally occurs in the winter season. The fruits are indehiscent, one seeded pod, and usually the pericarp is oily, sticky, and adhered to the seeds. Seeds are kidney-shaped and slightly pointed at posterior end (Shrestha *et al*., 2018), 2-4 mm long, 2-3 mm broad and 1-1.5 mm thick, chocolate brown to black color, and the seed coats are very hard (Datta and Das, 1970). Plants take 6-7 months in maturation. Fig. 1 shows the morphology of leaves, flowers and seeds of *P. corylifolia*. It has numerous uses as it is an important component of the allopathic and traditional system of medicines in various part of the world. It is also widely used in traditional Chinese medicine and traditional system of medicine in India such as Ayurveda, Siddha, Unani for the cure of psoriasis, leucoderma, and vitiligo (Khusboo *et al*., 2010). *P. corylifolia* is also known as 'Kusthanashini' or leprosy destroyer because of its ability to cure leprosy (Khusboo *et al*., 2010). The entire plant especially seeds, fruits and the volatile oil obtained from seeds are significantly used in the treatment of various diseases due to presence of high content of bioactive compounds. There are several bioactive constituents obtained from *P. corylifolia*, for example, psoralen, isopsoralen, bakuchiol, bakuchicin, bavachin, bavachinin, bavachalcone, isobavachalcone, daidzein genistein which belongs to various classes of secondary metabolites such as coumarins, furanocoumarins, meroterpenes, flavonoids, benzofurans, volatile oils and others (Zhang *et al*., 2016; Alam *et al*., 2018).

A wide range of abiotic stresses / elicitors have been found to alter the production of bioactive constituents by changing the

Fig. 1: Morphology of leaves, flowers and seeds of *Psoralea corylifolia*.

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aspects of secondary metabolism (Verpoorte *et al*., 2002). Various abiotic stresses or elicitors have been used for enhancement of secondary metabolite production in plant cells and suspension cultures (Hari *et al*., 2018). Linear furanocoumarins are found to be affected by changes in the environment and can be enhanced by the various environmental stresses (Dercks *et al*., 1990). It has been demonstrated that gamma radiation enhances the concentration of psoralen, a major furanocoumarin found in *P. corylifolia* (Jan *et al*., 2012). There are several literatures demonstrating the effect of various abiotic stresses and elicitors on the pharmaceutically important secondary metabolites of *P. corylifolia*. In these regards present review focuses on the important bioactive constituents and pharmaceutical activities of *P. corylifolia* and also summarizes the effects of various abiotic stresses or elicitors on bioactive constituents of *P. corylifolia*.

Pharmaceutical activities

P. corylifolia has been used since for a long time in traditional system of medicine for various purposes. It possesses several bioactive constituents that are mainly concentrated in the seeds and fruits. These bioactive constituents are extracted, and characterized by several researchers and possess various pharmaceutical activities which are discussed in the following sections:

Skin conditions

Phytoconstituents obtained from *P. corylifolia* possesses the abilities to treat various skin ailments such as psoriasis, vitiligo, leucoderma, eczemas. The antipsoriatic activity of ethanolic seeds extract of *P. corylifolia* was evaluated with the help of mouse tail models. Seeds extract showed an antipsoriatic activity of 75.8%, as compared to standard tazarot gel activity of 87.9%. Seeds extract converted the parakeratosis (keratinization) stage, which was the most important hallmark of psoriasis to the orthokeratosis (formation of anuclear keratin layer) stage of cell and thus confirmed its antipsoriatic activity (Dwarampudi *et al*., 2012). Extract of *P. corylifolia* seeds in hexane was formulated into a cream by using the stearic acid as a base, and utilized for the treatment of patients suffering from eczema in a clinical trial for a month. The parameters studied were exudation rate, length of the lesion, and rate of itching. The symptoms score decreased after two weeks of the application of the cream. The study concluded that *P. corylifolia* could be potentially used for the treatment of eczema (Beena *et al*., 2010). For the assessment of antipsoriatic activity and oxidative stress biomarkers properties, the effectiveness of babchi essential oil loaded nanocarrier gel was evaluated with the help of mouse tail models (Kumar *et al*., 2019).

Antimicrobial activity

The phytoconstituents psoralen, angelicin, bakuchicin and psoralidin obtained from the seeds were found to show antibacterial activity against gram-positive and gram-negative bacteria and among them mixtures of psoralen and angelicin showed stronger activity against gram-positive bacteria *Staphylococcus aureus* whereas psoralidin showed stronger activity against gram-negative bacteria *S. flexneri* and *S. sonnei* (Khatune *et al*., 2004). Monoterpenes such as Psoracorylifols (A-E) which were isolated from the seeds, possess inhibitory activity towards two strains (SS1 and ATCC 43504) of *Heliobacter pylori* (Yin *et al*., 2006). Purkayastha and Dahiya (2012) reported that babchi essential oil possesses antibacterial activity against multidrug-resistant bacterial strain. The problem of the development of multidrug resistance in pathogenic bacteria can be resolved by targeting the quorum sensing controlled virulence and biofilm formation in these bacteria. Husain *et al*. (2018) reported that methanolic fraction of *P. corylifolia* and its constituent bakuchiol reduced the quorum sensing regulated virulence and biofilm formation in *Chromobacterium violaceum*, *Pseudomonas aeruginosa, Serratia marcescens* and *Aeromonas hydrophila*. Methanolic seeds extract of *P. corylifolia* depict significant antifungal activity against dermatophytes *Trichophyton mentagrophytes, T. rubrum, Epidermophyton floccosum, Microsporum gypseum* which might be due to the presence of active metabolite 4-methoxy flavones (Prasad *et al*., 2004). Phenyl derivative of pyranocoumarin (PDP) extracted from petroleum ether extract of *P. corylifolia* showed potent antifungal activity against *Fusarium* species. Srinivasan and Sarada (2012) reported that acetylation of the C3 hydroxyl group of trichothecene mycotoxin by the trichothecene 3-O-acetyltransferase enzyme was responsible for the self defense mechanism of *Fusarium* species. PDP strongly binds with trichothecene 3-O-acetyltransferase and prevents the acetylation of C3 hydroxyl group of trichothecene resulted in the destruction of self-defense mechanism of *Fusarium* species.

In addition, bavachin isolated from *P. corylifolia* showed antiviral activity and was found to be highly effective against spring viraemia of carp virus (SVCV), which is an important pathogen of cyprinids. Bavachin inhibited the early event of SVCV replication *via* blocking SVCV induced apoptosis and cellular morphological damage (Cheng *et al*., 2018). In a study, Shoji *et al*. (2015) observed the anti influenza viral activity of bakuchiol by using Madin-Darby canine kidney cell and found that bakuchiol inhibited the viral infection and growth and decreased the expression of mRNA and protein in these cells.

Anti-inflammatory activity

Psoralidin obtained from the seeds inhibited the cyclooxygenases-2 (COX-2) and 5-lipoxygenase (5-LOX) pathway, and suppressed the ionizing radiation (IR)-induced expression of pro-inflammatory cytokines and ICAM-1 in human normal lung fibroblasts and mice (Yang *et al*., 2011). Phyto-constituents namely, bakuchiol, neobavaisoflavone, corylin, corylifol A, bavachin, bavachinin and isobavachalcone isolated from methanolic seed extract of *P. corylifolia* exhibited an inhibitory effect on IL-6-induced STAT3 promotor activation and phosphorylation in Hep3B cells (Lee *et al*., 2012). In a study carried out by Chen *et al*. (2017), twelve phytoconstituents such as 7-O-methylcorylifol A, 7-O-isoprenylneobavaisoflavone, 7-O-isoprenylcorylifol A, psoralen, isopsoralen, psoralidin, bakuchiol, 12,13-dihydro-12,13-epoxybakuchiol, p-hydroxybenzaldehyde, bavachalcone, mixture of b-sitosterol and stigmasterol were isolated from the fruits of *P. corylifolia*, and among them psoralen and 7-O-isoprenylcorylifol A were found to be most effective against the fMLP-induced superoxide anion generation and elastase release whereas bakuchiol, 12,13-dihydro-12,13-epoxybakuchiol, 7-O-isoprenylcorylifol A and psoralidin were most potent against LPS-induced NO generation. Hung *et al*. (2017) suggested that corylin, an isoflavonoid obtained from *P. corylifolia*, showed the anti-inflammatory properties and could be used as immunosuppressive drug for the cure of sepsis and septic shock.

Estrogenic activity

The estrogen receptor (ER) subtype-selective activities of the seeds extract of *P. corylifolia* and the compounds extracted from it were analyzed by Xin *et al*. (2010) using HeLa cells. The two furanocoumarins, psoralen and isopsoralen selectively activated

ER-α while others such as bavachin, neobavaisoflavone, corylifol A, isobavachalcone and bakuchiol activated both the ER-α and ER-β receptors (Xin *et al*., 2010). Various *in vitro* assays were performed by Lim *et al*. (2011) using *P. corylifolia* and reported that ethanolic seeds extract and its hexane fraction had most estrogenic activity and the constituent bakuchiol showed the highest estrogenic activity and ER binding affinity. In another study, Liu *et al*. (2014) observed that psoralidin obtained from ethyl acetate fraction of *P. corylifolia* could be a novel ER modulator and used as a promising candidate in alternative hormonal replacement therapies.

Neurodegenerative disorders

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is characterized by intraneuronal fibrillary meshwork and extracellular amyloid plaques in the brain. Amyloid β (A β) peptides abnormally accumulated and are believed to be accountable for the formation of amyloid plaque (Chen *et al*., 2013). Isobavachalcone and bavachinin obtained from *P. corylifolia* were found to reduce Aβ42-induced toxicity. Bavachinin inhibits fibrillarization whereas isobavachalcone significantly inhibits both oligomerization and fibrillarization of Aβ42 peptides in an SH-SY5Y cell model (Chen *et al*., 2013). The total prenylflavonoids obtained from the fruits of *P. corylifolia* inhibited the Aβ-42 peptides production, GSK-3β overactivation, hyperphosphorylation, proinflammatory cytokines production and oxidative stress and found to be a potential drug for the prevention of Alzheimer's disease in SAMP8 mouse model (Chen *et al*., 2018). Psoralen obtained from seeds inhibited the acetylcholinesterase (AChE) enzyme activity which leads to the inhibition of acetylcholine breakdown and helps in reduction of amyloid-beta (Aβ) peptides aggregation (Somani *et al*., 2015). In a study, Kim *et al*. (2016b) obtained seven components psoralen, angelicin, bavachinin, psoralidin, neobavaisoflavone, isobavachalcone, and bakuchiol from the ethanolic seeds extact of *P. corylifolia*, and among them bakuchiol was found to be most potent for the treatment of neurodegenerative disorders based on quantification and bio-efficacy analysis in hippocampal cell line HT22 and microglia cell line BV-2. In addition, Parkinson's disease is another neurodegenerative disorder in which microglia-mediated inflammatory responses perform an important role. MPTP (1-methyl-4-phenyl-1, 2, 3, 6- tetrahydropyridine) induced Parkinson's disease attenuated by the isobavachalcone isolated from *P. corylifolia*, which inhibited the activation of microglia through NF-κB Pathway in mice (Jing *et al*., 2017).

Neuroprotective

P. corylifolia seeds extract found to have a protective effect on palmitate- induced lipotoxicity in a neuron-like cell line, PC12 cells. It significantly attenuates palmitate-induced reactive oxygen species (ROS) generation and upregulated the mRNA expression levels of antioxidant genes. In addition, *P. corylifolia* seeds extract increased the cell viability and exhibited anti-apoptotic effects in palmitate-induced PC12 cells (Lee *et al*., 2016). It was believed that apoptosis caused by increased ROS generation performs a crucial role in pathogenesis of glaucoma (Kim *et al*., 2013). Bakuchiol obtained from *P. corylifolia* reduced the ROS mediated increase in apoptotic protein and has the neuroprotective effects on oxidative stress-induced retinal cell damage and might be considered as useful candidate in retinal diseases such as glaucoma (Kim *et al*., 2013). In another study, isobavachalcone was found to alleviate the neuronal injury in inflammation related brain diseases and this amelioration was carried out *via* inhibition of the lipopolysaccharide induced intercellular adhesion molecule-1 (ICAM-1) expression and leukocyte adhesion to brain endothelial cell through the blockage of toll-like receptor 4 (TLR4) signaling (Lee *et al*., 2015).

Anticancer activity

Apoptosis is one of the important mechanisms which were employed by several chemoprotective and antitumor drugs to exert their anticancer properties. Bakuchiol when applied in different concentration to human gastric cancer cell line NUGC3 in MTT cell viability assay, inhibited the cancer cell viability in concentration dependent manner. Further, bakuchiol treatment induced the caspase dependent apoptosis which involve PI3K/AKT and MAPK triggered signaling pathways (Lv and Liu, 2017). Li *et al*. (2016) suggested that bakuchiol possess both *in vitro* and *in vivo* estrogenic activity as well as anti-breast cancer activity and showed stronger anti-proliferative effects in breast cancer cells and induced intrinsic mitochondrial apoptotic pathway therefore bakuchiol might be used as a promising anti breast cancer drug (Li *et al*., 2016). In addition, bakuchiol enhances the tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) induced apoptosis *via* upregulation of TRAIL death receptors DR4 and DR5 and downregulation of survival protein through ROS/JNK mediated signaling pathway in colon cancer cell (Park *et al*., 2016). Psoralen and isopsoralen obtained from methanolic extract of *P. corylifolia* inhibited the growth of KB, KBv200, K562, K562/ADM cancer cells line and showed anti-cancer effect in dose-dependent manner (Wang *et al*., 2011). Ren *et al*. (2016) revealed that psoralidin inhibited the proliferation and induced the DNA damage of MCF-7, MDA-MB-231 and A549 cell lines in concentration dependent manner. Psoralidin was also found to induce the protective autophagy and ROS generation in MCF-7 cells. In biological systems NADPH oxidases (NOXs) is one of the main sources of ROS and play an important role in cancer chemotherapy. Further, it was found that psoralidin mediated NOX4 dependent increase in ROS formation contributed to the DNA damage and autophagy in MCF-7 cells (Ren *et al*., 2016). Table 1 summarizes the various bioactive constituents present in *P. corylifolia* and their pharmaceutical activities.

Effect of various abiotic stresses/ elicitors on bioactive constituents of *P. corylifolia*

Salt stress was found to influence the psoralen content and maximum increase has been reported at 25 mM NaCl (Katare *et al*., 2012). Gamma radiation also stimulated the content of furanocoumarins and phenylalanine ammonia lyase (PAL) activity of the seeds of *P. corylifolia*, irradiated with different doses (2.5, 5, 10, 15, and 20 kGy) in two successive generations G1 and G2 (Jan *et al*., 2012). Further, Jan *et al*. (2012) reported that concentration of psoralen and isopsoralen increased with increasing dose of gamma radiation. The content of psoralen and isopsoralen increased by 44.8% and 29.6% respectively compared to control at 20 kGy dose of gamma radiation in G_1 generation plants. GC–MS analysis of essential oil and volatile fraction of *P. corylifolia* seeds which were exposed to different doses of gamma radiation revealed that maximum oil content (1.6%) was found in seeds irradiated with 20 kGy gamma radiation as compared to control (0.9%). Plants raised from seeds exposed to 20 kGy dose showed the maximum increase in psoralen (49.3%), angelicin (26.4%), bakuchiol (54.1%), β-caryophyllene (39.8%), α-pinene (16.6%), camphene (149.4%), gerianal (132.2%) germacrene D (33.6%) and tricyclene (48.3%) (Jan

Table 1: Bioactive constituents and pharmaceutical activities of *P. corylifolia*.

Bioactive constituents	*Chemical nature of bioactive constituents*	*Pharmaceutical activities*	*References*
Psoralen	Furanocoumarin	Antibaterial, estrogenic, antidepressant, anti-inflammatory, anti-alzheimer's, anti-tumor	Khatune *et al*., 2004; Xu *et al*., 2008; Xin *et al*., 2010; Wang *et al*., 2011; Chen *et al*., 2017
Isopsoralen	Furanocoumarin	Antibacterial, anti-inflammatory, antidepressant, estrogenic, antitumor	Kong *et al*., 2001; Khatune *et al*., 2004; Xin *et al*., 2010; Wang *et al*., 2011; Chen *et al*., 2017
Bakuchiol	Meroterpene	Estrogenic, anticancer, neuroprotective, antibacterial, osteoblastic	Kim *et al*., 2008; Kim *et al*., 2013; Li *et al*., 2014; Lv and Liu, 2017; Husain *et al*., 2018
Bavachinin	Flavone	Anti-inflammatory, antialzheimer's,	Lee *et al*., 2012; Chen *et al*., 2013
Bavachin	Flavone	Osteoblastic, antiviral, anti- inflammatory, estrogenic	Wang *et al*., 2001; Xin *et al*., 2010; Lee *et al*., 2012; Cheng *et al*., 2018
Bakuchicin	Coumarin	Antibacterial, antitumor, hepatoprotective	Sun *et al*., 1998; Khatune *et al*., 2004; Kim *et al*., 2016a
Bavachalcone	Chalcone	Anticancer, CVS protective, anti-inflammatory	Shan *et al*., 2014; Dang *et al*., 2015
Isobavachalcone	Chalcone	Anti-inflammatory, antiparkinson, antialzheimer neuroprotective	Lee *et al*., 2012; Chen *et al*., 2013; Lee *et al*., 2015; Jing *et al*., 2017
Psoralidin	Coumarin	Estrogen receptor modulator, antidepressant, anticancer, anti-inflammatory	Chen *et al*., 2008; Yang *et al*., 2011; Liu *et al*., 2014; Ren *et al*., 2016
Daidzein	Isoflavone	Antioxidant, antidiabetic, topoisomerase inhibitor	Sun *et al*., 2003; Shinde *et al*., 2010
Genistein	Isoflavone	Antidiabetic, antiobesity, antioxidant	Shinde *et al*., 2010; Behloul and Wu, 2013
Corylin	Isoflavone	Osteoblastic, anti-inflammatory	Wang *et al*., 2001; Lee *et al*., 2012
Corylifol A	Isoflavone	Estrogenic, anti-inflammatory	Xin *et al*., 2010; Lee *et al*., 2012

et al., 2015). In a study by Bhat *et al*. (2015), treatment with alkylating agent ethyl methane sulphonate (EMS) leads to hyper accumulation of linear furanocoumarin psoralen at pre and post flowering stages for the attenuation of stress generated by ROS and the maintenance of high antioxidant potential of cells. Higher psoralen content was noticed with increasing dose and age of the plant. Psoralen content was 146.5% and 93.2% at pre and post-flowering stages respectively at 1% EMS (Bhat *et al*., 2015). In contrast Ali *et al*. (2008) reported decreased psoralen content of seeds by 86.7% compared to control under SO_2 stress condition. Cadmium as an abiotic elicitor leads to maximum phytoestrogenic isoflavone daidzein (1.74% dry weight) and genistein (0.23% dry weight) at the optimum 8 µM concentration and exposure time for 2 days in hairy root culture of *P. corylifolia* as compared to control (Satdive *et al*., 2014). Adventitious roots of *P. corylifolia* treated with methyl jasmonate and salicylic acid at dose of 30 and 150 µM L^{-1}, respectively were found to enhance the concentration of psoralen. Further, it was found that methyl jasmonate treated root samples showed better results (3.7 mg ml^{-1} of psoralen) than salicylic acid (0.015 mg ml^{-1}) and control plants (0.56 mg ml^{-1}) (Siva *et al*., 2014). In another study, salicylic acid at 1 mM concentration in the cell suspension culture of *P. corylifolia* stimulated the maximum accumulation of genistein (0.41% dry weight) and daidzein (3.4% dry weight) after 2 days of elicitation (Shinde *et al*., 2009).

Conclusions

P. corylifolia possess various pharmaceutical properties such as antimicrobial, anti-inflammatory, estrogenic, neuroprotective, anticancer, osteogenic activity, helps in various skin and neurodegenerative disorders. It is the relevant source of several valuable drugs, therefore elicitation of these valuable bioactive metabolites with an appropriate dose and exposure time of various abiotic stress factors / elicitors, has applications in the over-production of desired low yielded and high valued compounds, and an area of pharmaceutical and commercial importance.

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